Outcome of weekly carboplatin-paclitaxel based definitive chemoradiation in oesophageal cancer, in patients not considered suitable for platinum-fluoropyrimidine based treatment: a multi-centre, retrospective review.

Abstract

Background

Although cisplatin-fluoropyrimidine (CF) based definitive chemoradiotherapy (dCRT) is a standard of care for oesophageal cancer, toxicity is significant and limits its use in elderly and frail patients. The weekly carboplatin/paclitaxel (wCP) based dCRT provides a viable alternative, although prospective data is lacking in the dCRT setting.

Methods

In this multicentre retrospective study from 9 radiotherapy centres across the United Kingdom, we evaluated outcome in patients who had non-metastatic, histologically confirmed carcinoma of the oesophagus (adenocarcinoma, squamous-cell, or undifferentiated; WHO performance status 0–2; stage I–III disease) and had been selected to receive wCP based dCRT as they were considered not suitable for CF dCRT. dCRT consisted of Carboplatin AUC 2 and Paclitaxel 50mg/ m^2 (days 1,8,15,22,29) and the recommended radiation dose was 50Gy in 25 daily fractions. We assessed overall survival (OS), progression free survival (overall, local and distant) (PFS), proportion of patients failure-free at response assessment (12 weeks post dCRT), treatment compliance and toxicity.

Findings

214 patients from 9 UK centres were treated between Feb 15, 2013, and March 19, 2019. 39.7% of patients were ≥75yrs ; 18.7% ≥80 yrs. Indications for wCP dCRT were co-morbidities (47.2%), clinician choice (36.4%) and poor tolerance/progression on CF induction chemo (15.8%). Median OS was 24.28 months (95% CI: 20.07-30.09) and median PFS was 16.33 months (95% CI: 14.29-20.96). Following treatment, 69.1% (96/139) had combined complete response (CR) on endoscopy with non-progression (CR/partial response (PR)/stable disease (SD)) on imaging. The 1-year and 2-year OS for this patient group was 81.9% (95% CI: 75.6%-86.8%) and 50.6% (95% CI: 40.5%-60.0%) respectively. 33% (n=70) of patients experienced at least one grade 3+ acute toxicity (Grade 3/4 haematological:10%; grade 3/4 non-haematological:32%) and there were no treatment related deaths. 86.9% of patients completed at least 4 cycles of concomitant wCP chemotherapy and planned radiotherapy was completed in 97.7% (209/214).

Conclusion

Weekly carboplatin-paclitaxel based chemoradiotherapy appears to be well tolerated in elderly patients and in those with co-morbidities, where CF-based dCRT is contra-indicated. Survival outcomes are comparable to CF-based dCRT.

Introduction

Definitive chemoradiotherapy (dCRT), usually consisting of radiation dose 50-64 Gray (Gy) in 1.8-2Gy per fraction, is a treatment option for patients with localised oesophageal cancer, particularly squamous cell cancers (SCC) and in patients [both SCC and adenocarcinoma (ACA)] where surgery is considered inappropriate due to patient's co-morbidities or disease extent. Traditionally, a combination of cisplatin with 5FU (or capecitabine) (CF), has formed the chemotherapy backbone [i],[ii], but more recently a combination of weekly carboplatin-paclitaxel (wCP) has been reported in retrospective studies to demonstrate comparable efficacy to cisplatin–fluoropyrimidine (CF) with better tolerance and lower incidence of grade 3-4 toxicity[iii]. This regimen, originally reported in the neo-adjuvant setting in the CROSS trial[iv], demonstrated a low incidence of Grade 3-4 toxicity (hematological 8%; non-hematological 13%) and has therefore allowed physicians to treat with radical intent, patients who would have otherwise been considered unfit for radical treatment – mainly those with poor performance status or elderly patients who are unlikely to withstand the traditional CF radiation combination.

In the UK, a national survey of upper GI oncologists demonstrated that whilst the majority of oncologists still favoured the CF based dCRT for patients who were fit enough to receive it, wCP dCRT was commonly offered in patients where CF-dCRT was contraindicated because of age, frailty or medical comorbidities. Herein we report the results of a national, multi-centre retrospective review of outcome in patients treated with wCP based dCRT.

Methods

Study design and patients

In this multi-centre retrospective study, we included patients from radiotherapy (RT) centres across the UK who met the following key eligibility criteria: non-metastatic, histologically confirmed carcinoma of the oesophagus or gastro-oesophageal junction (GOJ), WHO performance status 0-2, stage I-III disease and who, in the opinion of the treating clinician, were not suitable for CF-based dCRT. The RT centres were primarily identified based on the respondents of a national survey[v]..

Patients were staged in accordance with local protocols, which in the UK, consists of contrast-enhanced spiral CT scan of thorax and abdomen, ^{18}F-fluorodeoxyglucose CT-PET (PET-CT), endoscopic

ultrasound where feasible, and optional laparoscopy in patients with tumour extending below the diaphragm.

Treatment and follow up

Chemotherapy consisted of weekly carboplatin (AUC2) and paclitaxel (50mg/m2) given intravenously concurrent with radiotherapy. Patients who had received induction chemotherapy prior to start of wCP dCRT were also included in the study. Dose modification for toxicity was as the discretion of treating clinician.

RT was delivered as per local protocol. The usual dose of radiation was 50Gy in 25 fractions, delivered Monday to Friday as three-dimensional (3D) conformally planned or intensity modulated (including volumetric arc) radiotherapy. Follow up assessment included a CT scan (or PET-CT, depending on centre choice) at 12 weeks following completion of dCRT; endoscopic assessment of response was also routinely conducted in 7 of 9 centres which contributed to this study. Subsequent follow up was as per centre choice, but data was collected on overall survival, progression free survival, site of disease relapse and acute toxicity.

Endpoints were overall survival, progression free survival (overall, local and distant), proportion of patients failure-free at response assessment (12 weeks post dCRT), treatment compliance and acute toxicity.

Statistical analysis

All statistical analyses were conducted using the Stata 14 statistical package according to a pre-specified analysis plan. Survival was calculated from the date of diagnosis to when an event occurred, that is, any death for overall survival (OS), and local/distant progression or any death for local/metastasis progression free survival (PFS). Local PFS was defined as the time to progression within the radiotherapy field (with or without metastatic disease) or death due to any cause. Distant PFS was defined as time to progression with metastases or death by any cause. Patients who were event free were censored at the time they were last known to be event free. The Kaplan Meier method was used to derive estimates of event time distributions for OS and overall, local and distantPFS. Hazard ratios from univariable and multivariable Cox regression models were assessed for OS of all patients and also for patients that reached and received the post treatment endoscopy (the proportional hazards assumption for each model was tested using Cox-Snell residuals and Schoenfeld's global test).

The multivariable Cox regression models included Age (<75 vs ≥75), Sex (Female vs Male), WHO PS (0 vs 1-2), T stage (1-2 vs 3-4), N stage (0 vs 1+), Induction chemo (Yes vs No), Histology (SCC vs Adeno), Site (middle/upper Third vs Lower Third), Post treatment response (Complete Response (CR)

on endoscopy with CR/Stable disease (SD)/Partial response (PR) on imaging vs Others) and Disease length (continuous variable).

Source of funding

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Results

Study population

214 patients from 9 UK centres who received dCRT between Feb 15, 2013, and March 19, 2019, were included in the analysis. Patient characteristics are described in Table 1. In summary, median age was 73 (range 42-91; 39.7% ≥75yrs; 18.7% >80 yrs), 65.0% (139/214) were male, only 29.0% (62/214) were WHO Performance Status 0, 57.5% (123/214) had adenocarcinoma and median disease length was 4.7cm (IQR: 3.0-6.5).

Of the 214 patients, 38.3% (82/214) received induction chemotherapy. Indications for wCP dCRT included co-morbidities (47.2%, n=101), clinician preference (36.4%, n=78) and poor tolerance/progression on CF induction chemo (15.8%, n=34). During dCRT (Figure 1 and Table 1), the median percentage of dose of both carboplatin and paclitaxel was 100 (IQR: 80-100). 87.4% and 62.1% of patients completed 4 and 5 cycles of carboplatin respectively, whilst 86.9% and 61.7% of patients completed 4 and 5 cycles of paclitaxel. In 61.7% (n=132) of patients, radiation was planned using IMRT. The majority of patients were prescribed 50Gy/25 fractions or above (dose range 41.4Gy/23fractions-64Gy/32 fractions with 2 patients being prescribed <50 Gy: 1 each were prescribed 41.4Gy and 45Gy respectively and were included in the analysis as neither patient was fit for surgery). Planned radiotherapy was completed in 97.7% (209/214).

The median duration of follow-up for surviving patients was 16.9 months (95% CI: 15.6, 19.5)).

Toxicities

All toxicities (graded as per CTCAE version 4) reported during dCRT are shown in Table 2. During treatment 32.7% (n=70) of patients experienced at least one grade 3+ toxicity; 9.8% (n=21) had at least 1 grade 3/4 *haematological* toxicity and 31.8% (n=68) had at least 1 grade 3/4 *non-haematological* toxicity. The most common grade 3 non-haematological toxicities were nausea (6.1%, n=13) and vomiting (6.1%, n=13). There were 2 recorded deaths during treatment (oesophageal haemorrhage, duodenal perforation) but these were not felt to be treatment related. There were 10 further deaths within 90 days of treatment; 4 were due to progressive metastatic disease, 1 due to hospital acquired

pneumonia, 1 due to pulmonary embolism, 1 to unrelated fall and head injury and 3 from unknown causes.

Commented [MOU1]: In the patient with PE and Pneumonia, Do you know the approximate time point of death compared to completion of treatment (if they were say >6 weeks after completion of treatment, we can say that these were unlikely to be direct consequences of treatment). The others are clearly not related.

Overall & Progression Free Survival

Median overall survival was 24.3 months (95% CI: 20.07-30.09), demonstrated in Figure 2a. The 1-year and 2-year OS rates were 81.9% (95% CI: 75.6%-86.8%) and 50.6% (95% CI: 40.5%-60.0%) respectively. The univariable Cox proportional hazards regression models (Table 3) showed that the significant predictors of worse OS were higher N Stage (HR: 2.01 (95% CI: 1.20-3.36, p=0.008)), having induction chemotherapy (HR: 1.63 (95% CI: 1.03-2.56, p=0.037)) and disease length (HR 1.13 (95% CI: 1.02-1.26,p=0.021)), but they were all statistically insignificant (p>0.05) after adjusting for baseline characteristics in the multivariable model. In addition, whilst 36% of patients received carboplatin-paclitaxel chemotherapy based upon 'clinician choice', there was no statistically significant difference in OS between those patients, and those whose indication for carboplatin-paclitaxel was due to co-morbidities or poor tolerance/progression to induction chemotherapy.

At the post-treatment response assessment, 139 patients had an endoscopy, 189 had cross-sectional imaging, and 12 patients had died prior to the assessment time point. 71.2% (99/139) had complete response (CR) on endoscopy defined as a negative biopsy, 86.2% (163/189) had non-progression (CR/Partial response (PR)/Stable disease (SD)) on imaging, and 72.1% (98/136) had combined CR on endoscopy with non-progression on imaging (in the cohort where both endoscopy and imaging available, n=136). The OS analysis for patients that proceeded to post treatment endoscopy (139/214) (Table 4 and Figure 2b) showed that the median survival in patients that had complete response (CR) on the endoscopy plus non-progression on imaging, i.e. "treatment failure free" (98/139) was 30.1 months (95% CI: 27.0-.), compared to 16.9 months (95% CI: 14.2-22.6) for those who did not i.e. "those with evidence of residual or progressive disease. The 1-year and 2-year OS for patients that were "treatment failure free" were 92.2% (95% CI: 85.5%-95.8%) and 60.2% (95% CI: 47.3%-70.9%) respectively. The hazard ratio for treatment failure free vs failure was significant in both univariable and multivariable analyses (3.86 (95% CI: 2.04-7.33, p<0.001) and 5.07 (95% CI: 2.11-12.21, p<0.001) respectively).

Of the 214 patients treated, 33.2% (71/214) had progressed at the time of data collection, with 40.8% (29/71) of those being local, 52.1% (37/71) distant and 7.0% (5/71) both local and distant relapses (missing data, n=5). Median PFS was 16.3 months (95% CI: 14.3-21.0), median local PFS was 20.1 months (95% CI: 16.8-22.9) and median distant PFS was 21.0 months (95% CI: 16.7-30.1) (Figure 2c).

Figure 1 – Percent of total chemotherapy dose during CRT

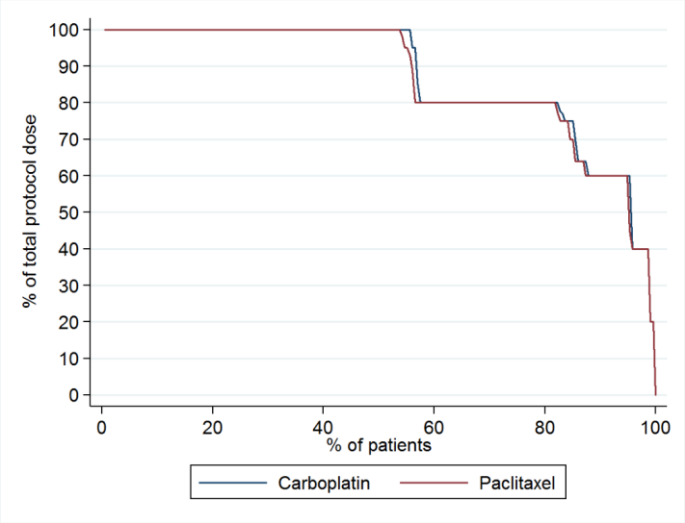
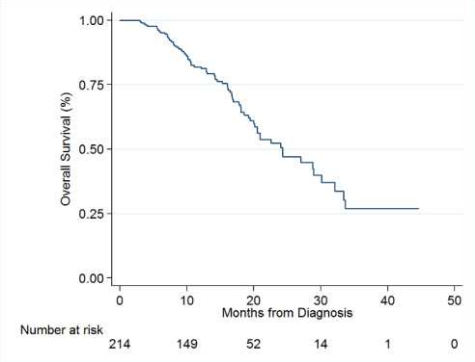
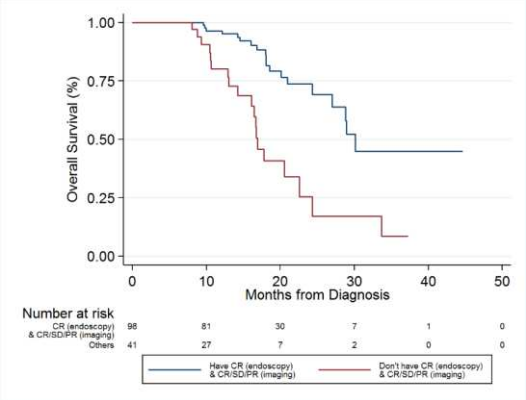


Figure 2 – Kaplan-Meier curves of overall and progression free survival

(a)



(b)



(c)

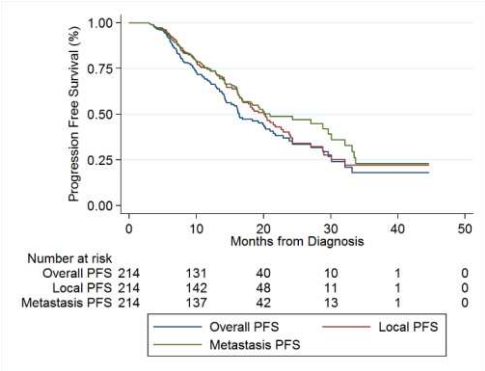


Table 1 – Patient characteristics and treatment

Characteristic		n	%
Sex	Male	139	65.0%
	Female	75	35.0%
Age	Median (IQR, range)	73 ((65,78), 42-91)	
	70+	134	62.6%
	80+	40	18.7%
T stage	1	8	3.7%
	2	48	22.4%
	3	124	57.9%
	4	29	13.6%
	Missing	5	2.3%
N stage	0	97	45.3%
	1	80	37.4%
	2	32	15.0%
	3	5	2.3%
Site	Lower third/GOJ	123	57.5%
	Middle third	79	36.9%
	Upper third	12	5.6%
Performance status	0	62	29.0%
	1	124	57.9%
	2	23	10.7%
	Missing	5	2.3%
Disease length	Median (IQR, range)	4.7 ((3.0, 6.5), 1-13)	
Histology	SCC	91	42.5%
	Adeno	123	57.5%
Indication for carboplatin-paclitaxel	Co-morbidities precluding cisplatin/5-FU combination	101	47.2%
	Clinician choice	78	36.4%
	Poor tolerance to induction chemotherapy	17	7.9%
	Progression following induction chemotherapy	17	7.9%
	Missing	1	0.5%
Induction chemotherapy	Yes	82	38.3%
	No	132	61.7%
RT planning	Conformal	54	25.2%
	IMRT/Rapid arc	132	61.7%
	Missing	28	13.1%
Radiotherapy regimen	41.4Gy in 23#	1	0.5%
	45Gy in 25#	1	0.5%
	50Gy in 25#	179	83.6%
	50.4Gy in 28#	5	2.3%
	54Gy in 30#	21	9.8%
	60Gy in 30#	1	0.5%
	64Gy in 32#	1	0.5%
	Not completed*	5	2.3%
Concurrent Carbolatin/Paclitaxel	Carboplatin dose intensity (median, IQR, range)	100 ((80, 100), 0-100)	
	Completed 4 cycles of Carboplatin	187	87.4%
	Completed 5 cycles of Carboplatin	133	62.1%
	Paclitaxel dose intensity (median, IQR, range)	100 ((80, 100), 0-100)	
	Completed 4 cycles of Paclitaxel	186	86.9%
	Completed 5 cycles of Paclitaxel	132	61.7%
Reasons for non-completion of concurrent chemotherapy	Nausea	8	3.7%
	Vomiting	6	2.8%
	Neutropenia	26	12.1%

Carboplatin/Paclitaxel	Infection	6	2.8%
	Dehydration	7	3.3%
	Diarrhoea	3	1.4%
	Fatigue	3	1.4%
	Oesophagitis	4	1.9%
	Thrombocytopenia	11	5.1%
	Hypotension	2	0.9%
	Other	18	8.4%

*1x21.6Gy, 2x36Gy, 1x48Gy, 1x48.6Gy

Table 2 – Toxicities during CRT (N=214)(CTCAE v4)

Toxicity	**Grade**									
(N=214)	1	%	2	%	3	%	4	%	5	%
Blood/lymph										
Anaemia	16	7.5%	15	7.0%	3	1.4%	0	0.0%	0	0.0%
Febrile Neutropenia	2	0.9%	9	4.2%	14	6.5%	0	0.0%	0	0.0%
Neutropenia	4	1.9%	9	4.2%	5	2.3%	0	0.0%	0	0.0%
GI disorders										
Abdominal pain	1	0.5%	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Constipation	13	6.1%	3	1.4%	2	0.9%	0	0.0%	0	0.0%
Duodenal perforation	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.5%
Diarrhoea	12	5.6%	5	2.3%	5	2.3%	0	0.0%	0	0.0%
Dysphagia	8	3.7%	4	1.9%	1	0.5%	0	0.0%	0	0.0%
Gastrointestinal haemorrhage	0	0.0%	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Mucositis oral	1	0.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Nausea	30	14.0%	15	7.0%	13	6.1%	0	0.0%	0	0.0%
Oesophagitis	36	16.8%	37	17.3%	12	5.6%	0	0.0%	0	0.0%
Oesophageal pain	0	0.0%	4	1.9%	0	0.0%	0	0.0%	0	0.0%
Oesophageal haemorrhage	0	0.0%	1	0.5%	0	0.0%	0	0.0%	1	0.5%
Pancreatitis	0	0.0%	0	0.0%	1	0.5%	0	0.0%	0	0.0%
Upper gastrointestinal haemorrhage	0	0.0%	0	0.0%	1	0.5%	0	0.0%	0	0.0%
Vomiting	23	10.7%	6	2.8%	13	6.1%	0	0.0%	0	0.0%
General disorders										
Edema limbs	1	0.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Fatigue	42	19.6%	25	11.7%	7	3.3%	0	0.0%	0	0.0%
Pain	15	7.0%	11	5.1%	1	0.5%	0	0.0%	0	0.0%
Infections										
Infection	3	1.4%	8	3.7%	9	4.2%	0	0.0%	0	0.0%
Joint infection	0	0.0%	0	0.0%	1	0.5%	0	0.0%	0	0.0%
Sepsis (non-neutropenic)	0	0.0%	0	0.0%	2	0.9%	0	0.0%	0	0.0%
Wound infection	0	0.0%	0	0.0%	1	0.5%	0	0.0%	0	0.0%
Urinary tract infection	0	0.0%	0	0.0%	1	0.5%	0	0.0%	0	0.0%
Investigations										
Platelet count decreased	10	4.7%	7	3.3%	1	0.5%	0	0.0%	0	0.0%
Weight loss	0	0.0%	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Metabolism/nutrition										
Anorexia	2	0.9%	3	1.4%	3	1.4%	1	0.5%	0	0.0%
Dehydration	1	0.5%	4	1.9%	12	5.6%	0	0.0%	0	0.0%
Nervous system disorders										
Extrapyramidal disorder	0	0.0%	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Peripheral sensory neuropathy	1	0.5%	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Renal and urinary disorders										
Acute kidney injury	0	0.0%	0	0.0%	1	0.5%	0	0.0%	0	0.0%
Chronic kidney disease	0	0.0%	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Respiratory, thoracic and mediastinal disorders										
Dyspnoea	2	0.9%	2	0.9%	0	0.0%	0	0.0%	0	0.0%
Skin										
Alopecia	1	0.5%	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Vascular disorders										
Thromboembolic event	9	4.2%	10	4.7%	4	1.9%	0	0.0%	0	0.0%

Table 3 - Univariable and multivariable cox regression analysis of overall survival (OS) by baseline characteristics in all patients (N=214)

		OS (months)**			Univariable			Multivariable (n=195)		
		n	Median	95% CIs	HR	95% CIs	p	HR	95% CIs	p
Age	<75	129	20.5	(18.0, 27.0)	1.00			1.00		
	≥75	85	28.9	(21.0, -)	0.63	(0.38, 1.05)	0.077	0.65	(0.37, 1.17)	0.366
Sex	Female	75	32.1	(16.9, -)	1.00			1.00		
	Male	139	24.0	(20.0, 28.9)	1.08	(0.66, 1.77)	0.748	1.06	(0.58, 1.91)	0.858
WHO PS	0	62	28.9	(18.0, -)	1.00			1.00		
	1-2	147	24.3	(19.2, 32.1)	1.08	(0.66, 1.75)	0.770	1.30	(0.73, 2.32)	0.370
T stage	1-2	56	-	(19.2, -)	1.00			1.00		
	3-4	153	22.6	(18.5, 30.1)	1.69	(0.93, 3.09)	0.086	1.03	(0.52, 2.04)	0.926
N stage	0	97	28.9	(24.0, -)	1.00			1.00		
	1+	117	20.5	(17.8, 24.3)	2.01	(1.20, 3.36)	0.008	1.78	(0.95, 3.34)	0.074
Induction chemo	N	132	28.8	(22.6, 33.4)	1.00			1.00		
	Y	82	19.2	(16.7, 24.3)	1.63	(1.03, 2.56)	0.037	1.53	(0.89, 2.65)	0.126
Histology	Squamous cell carcinoma(SCC)	91	32.1	(18.0, -)	1.00			1.00		
	Adenocarcinoma	123	22.6	(20.0, 28.9)	1.09	(0.69, 1.73)	0.713	1.05	(0.53, 2.05)	0.891
Site	Mid Third/ Upper Third	91	32.1	(18.0, -)	1.00			1.00		
	Lower Third	123	24.0	(20.1, 28.9)	1.10	(0.69, 1.74)	0.698	0.91	(0.48, 1.74)	0.782
Indication for Carboplatin/ Paclitaxel	Non-progressors	196	24.3	(20.1, 30.1)	1.00			1.00		
	Progressors	17	-	(8.1, -)	1.12	(0.51, 2.44)	0.783	0.53	(0.20, 1.44)	0.213
Disease length - mean (sd)		4.91 (2.27)			1.13	(1.02, 1.26)	0.021	1.11	(0.99, 1.26)	0.085

*HRs calculated for every 1cm increase

**From diagnosis

Table 4 – Univariable and multivariable cox regression analysis of overall survival (OS) by baseline characteristics in patients that reached and received the post treatment endoscopy (N=139)

		OS (months)**			Univariable			Multivariable (n=124)		
		n	Median	95% CIs	HR	95% CIs	p	HR	95% CIs	p
Age	<75	83	24.3	(18.0,-)	1.00			1.00		
	≥75	56	28.9	(21.0,-)	0.73	(0.37,1.44)	0.358	1.09	(0.48,2.47)	0.829
Sex	Female	47	33.7	(16.9,-)	1.00			1.00		
	Male	92	27.0	(20.5,-)	1.03	(0.52,2.05)	0.926	1.48	(0.58,3.75)	0.411
WHO PS	0	46	28.9	(20.1,-)	1.00			1.00		
	1-2	89	27.0	(21.0,-)	1.12	(0.58,2.16)	0.743	1.47	(0.59,3.65)	0.412
T stage	1-2	41	-	(20.1,-)	1.00			1.00		
	3-4	93	24.3	(20.5,33.7)	1.69	(0.74,3.88)	0.215	0.92	(0.36,2.34)	0.854
N stage	0	70	28.9	(20.1,-)	1.00			1.00		
	1+	69	24.3	(18.0,33.7)	1.70	(0.86,3.38)	0.130	1.08	(0.45,2.62)	0.863
Induction chemo	N	89	28.8	(24.3,-)	1.00			1.00		
	Y	50	20.5	(16.9,33.7)	1.86	(1.00,3.55)	0.060	1.33	(0.60,2.97)	0.487
Histology	Squamous cell carcinoma(SCC)	56	-	(18.5,-)	1.00			1.00		
	Adenocarcinoma	83	27.0	(20.5,33.7)	0.95	(0.50,1.82)	0.879	0.53	(0.19,1.43)	0.208
Site	Mid Third/ Upper Third	56	-	(18.5,-)	1.00			1.00		
	Lower Third	83	27.0	(20.5,33.7)	1.09	(0.57,2.08)	0.802	0.95	(0.36,2.45)	0.909

Post treatment Response	CR (endoscopy) & CR/SD/PR (imaging)	98	30.1	(27.0,-)	1.00			1.00		
	Others	41	16.9	(14.2,22.6)	3.86	(2.04,7.33)	<0.001	5.07	(2.11,12.21)	<0.001
Disease length* - mean (sd)		4.71 (2.13)			1.10	(0.94,1.29)	0.231	1.05	(0.86,1.28)	0.659

*HRs calculated for every 1cm increase
**From diagnosis

Discussion

This UK multicentre retrospective cohort evaluated the outcome of wCP based dCRT in 'borderline fit/risk adverse' patients. Forty percent of the patients were 75 years or older, (18.7% ≥ 80 years), 63% had either significant comorbidities at baseline or had progression/intolerance to induction chemotherapy and nearly 60% of the patients had ACA. The median OS was 24.3 months with an overall Grade 3-4 toxicity rate of 33% during dCRT. Following treatment, patients who had complete response (CR) on the endoscopy plus non-progression (CR/PR/SD) on imaging ("failure free") had the best outcome with 1-year survival of ~92% and a 2-year survival of ~60%

Study in the context of current literature

There are no published randomised trials assessing the role of wCP chemotherapy concurrent with definitive radiotherapy in oesophageal cancer. The CROSS trial utilised wCP in the neoadjuvant setting and demonstrated that this combination was well tolerated, with low haematological and non-haematological toxicity (toxicity grade ≥3 7% and 13% respectively), and a pathological complete response rate of 29%. Based on these results several retrospective studies have assessed this combination in the definitive setting. Table 5 provides a comparison with other reported studies. Prior to our series, the largest retrospective study by Versteijne et al[vi] included 184 patients and demonstrated a median OS 16.8 months. However, no acute or long term toxicity was reported in this paper and a quarter of patients did not complete the chemotherapy. It, however, confirmed that 41% developed locoregional recurrence post treatment (median follow-up 22.8 months), the majority at the site of the primary tumour, which is comparable to our locoregional recurrence data. The study by Noronha et al[vii] also included a similar number (n=179) and reported a median OS of 19 months. However, 92% of patients had SCC histology and only 15% of patients had tumours in the distal oesophagus/GOJ. In addition, 56% of patients developed ≥grade 3 toxicity with a high incidence of neutropenia (12%) and

infection (11%). In most of the other studies, SCC was the prevalent histology, unlike our series, where 57% of the patients had ACA. The only study reporting outcomes in patients with predominantly ACA histology was the series published by Haj Mohammed et al[viii], and included 127 patients, categorised as either being medically inoperable due to comorbidities, or irresectable due to tumour stage. They reported a median OS of 17.1 months. The study demonstrated that toxicity (grade ≥3 toxicity 44%) and tolerance to chemotherapy was significantly worse in medically inoperable patients compared to those irresectable due to tumour stage (median age 72 years). The majority of other reported retrospective studies also have a younger median age of patients. Only one small retrospective study by Kelly et al[ix] assessed wCP with definitive radiotherapy in an elderly population (aged ≥70). It confirmed that this regimen is well-tolerated although numbers were small (n=27).

TABLE 5 SUMMARY OF PUBLISHED STUDIES

AUTHORS	Study type	N	Age	Histology	Rtx dose	Toxicity	OS
OWENS ET AL (2019)	Retrospective	N=214	Median age 73	42.5% SCC	50Gy in 25 fractions	33% ≥grade 3 toxicity	Median OS 24.3 months
WANG ET AL (2007)[x]	Phase II	N=50	Median age 60	33% SCC	45Gy in 25 fractions	Neutropenia 23%	Median OS >44 months (n=16)
MEERTEN ET AL (2010)[xi]	Phase II (abstract)	N=52	Not reported	70% SCC	Not reported	Grade ≥ 3: neutropenia 16%, esophagitis 12%, fatigue 8%,	Median OS 17 months
KELLY ET AL (2013)	Retrospective	N=27	All aged over 70	56% SCC	Not reported	Not reported	At 11 months, 55% alive
VERSTEIJNE ET AL (2014)	Retrospective	N=184	Median age 66	52% SCC	50.4Gy in 28 fractions	Not reported	Median OS 16.8 months
HAJ MOHAMMAD (2014)	Retrospective	N=127	Mean age 63	46% SCC	50.4Gy/28	27% ≥grade 3 toxicity	Median OS 17 months
NORONHA ET AL (2016)	Retrospective	N=179	Median age 54	92% SCC	Mean 58.7Gy/32	56% ≥grade 3 toxicity	Median OS 19 months
ARAUJO ET AL (2016)[xii]	Retrospective	N=46	Median age 62	83% SCC	50.4Gy in 28 fractions	13% fatigue	Median OS 13.4 months
XIA ET AL (2017)[xiii]	Phase II	N=65	Mean age 61	90% SCC	50.4Gy/28 or 61.2Gy/34	28% ≥grade 3 toxicity	Median OS 21.7 months
VAN RULER ET AL (2017)[xiv]	Retrospective	N=66	Median age 69	59% SCC	50.4Gy in 28 fractions	61% adverse event grade ≥3	Median OS 13.1 months. 2 year OS 30%
HONING ET AL (2014)	Retrospective (comparison to cis-5FU)	N=55	Median age 65	58% SCC	Median dose 50.4 Gy	21% ≥grade 3 toxicity	Median OS 13.8 months
QU ET AL (2017)[xv]	Retrospective (comparison to	N=26	Median age 76	35% SCC	50Gy in 25 fraction	38% ≥grade 3 toxicity	Median OS 15 months

	cis/5FU or carbo/5FU)						
MUNCH ET AL (2018)[xvi]	Retrospective (comparison to cis/5FU)	N=22	Median age 68	100% SCC	Median dose 59.4Gy/33	Myelotoxicity ≥ grade 3 55%	1 year OS 70%

Our study is one of the largest studies evaluating the use of wCP for dCRT in oesophageal cancer and the first from the UK, and demonstrates that outcomes and toxicities are consistent with current literature, and reproducible in a multi-centre setting. Secondly, this pragmatic study, predominantly in an elderly population, has selectively looked at patients who would otherwise be considered unsuitable for radical CRT - a patient population which we frequently encounter in day to day practice, but which is not well represented in clinical trials. This study assures us that survival in this patient group is comparable to that seen in younger/fitter patients. Thirdly, >50% of the patients had adenocarcinoma and >50% had distal oesophageal or junctional tumours, which is reflective of patient distribution in western populations. As discussed, the study by Versteijne et al, whilst comparable to our study population, demonstrated a median OS of 16.8 months overall with a statistically significant improvement in OS in squamous histology vs adenocarcinomas (20.5 months vs 14.7 months p=0.046). The majority of other large retrospective studies also had a significantly higher number of patients with squamous histology. Despite these differences and the perceived better response/survival in SCC, our data suggests that equivalent survival and response rates can be achieved in an ACA predominant population. Finally, this study lends further support to the use of 12-week post-treatment response criteria as a surrogate for overall survival, as originally reported in the SCOPE-1 trial[xvii]. Patients who were failure free at response evaluation had a statistically superior OS compared to those who were not failure free (30.1 months vs 16.9 months). Our data also demonstrated that locoregional recurrence occurred in 41% of patients, comparable to published studies. The prospective ART-DECO study is assessing the use of weekly carboplatin-paclitaxel dCRT and randomising between standard dose radiotherapy (50.4Gy in 28 fractions) versus a dose escalation arm with a simultaneous integrated boost to the primary tumour (total dose 61.6Gy in 28 fractions). The aim of this study is to assess if dose escalation will improve local tumour control and thus overall survival. In the ongoing SCOPE2 study (https://clinicaltrials.gov/ct2/show/NCT02741856), patients with an inadequate Day 14 PET-CT response are being randomised to continuing cisplatin-capecitabine as concurrent chemotherapy versus switch to carboplatin-paclitaxel regimen. Radiotherapy dose escalation (50Gy/25 fractions vs 60Gy/25 fractions) is also being evaluated in the study.

Limitations

The biggest limitation of the current study is its retrospective nature, and there is likely to be under-reporting, particularly of toxicity data and late sequelae from treatment. The study was not randomised but, as discussed, prospective randomised comparison to standard cisplatin-5FU chemotherapy is unlikely to be assessed in the future due to the perceived equipoise of the two regimens. Although we aimed to include 'high risk' patients only, an element of selection bias is inevitable. Notably, 36% of the patients received this treatment as "clinician choice" suggesting decisions regarding fitness may

have been made subjectively in a proportion of patients although as noted, survival of this patient group was not significantly different to others. Geriatric assessment tools are not routinely used in assessment of elderly cancer patients, but with increasing life expectancy and the increasing treatment options in oncology, onco-geriatric assessments need to become integral part of cancer care. Indeed, the phase I-II OSAGE trial specifically aims to look at outcomes from wCP dCRT in the over-75 patient group, and incorporates formal geriatric evaluation[xviii].

Another short-coming is the relatively short follow-up (median FU alive patients of 16.89 months). However, this is similar to the median follow up in the initial report from the SCOPE-1 trial (16.8 months), and shows comparable outcomes at this data point (median OS 25.4 months vs 24.3 months). The proportion of patients who were treatment failure free at 12 weeks post treatment was 76.9% in SCOPE1 and 72.1% in the cohort reported here. However, reported grade 3/4 toxicities in the dCRT arm in SCOPE-1, were significantly higher (28% haematological toxicity and 63% non-haematological) although this data was prospectively gathered in comparison to our study.

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Conclusion

Weekly carboplatin-paclitaxel based chemoradiotherapy appears to be well tolerated in elderly patients and in those with co-morbidities, where CF-based dCRT is not appropriate. Treatment outcomes are promising and support the use of this regimen in clinical practice. Outcomes from prospective trials are awaited and, pending regulatory approval, the use of weekly carboplatin-paclitaxel is being incorporated as one of the study arms in the prospective SCOPE-2 trial[xix] albeit in a select patient group (non-responders at day 14 PET/CT assessment).

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